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A COMPARATIVE MICROSCOPIC STUDY OF THE MELANIN CONTENT OF PIGMENTED SKINS WITH SPECIAL REFERENCE TO THE QUESTION OF COLOR INHERITANCE AMONG MULATTOS

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INTRODUCTORY, WITH A STATEMENT OF PROBLEMS INVOLVED

THE comparative histologic study of pigmented skins was undertaken with the hope of discovering evidence that might throw more light on the problem of color inheritance among the descendants of crosses between whites and negroes. The primary point at issue, until very recently, was whether human skin color in inheritance conformed more closely to the alternative (Mendelian), or the blended scheme; or perhaps to the ancestral (Galtonian) scheme. The studies of G. C. and C. B. Davenport show conclusively that there is a measure of segregation among the individuals of the third generation, hence a Mendelian-like inheritance.

This study, suggested to me by the above-mentioned investigators, is, consequently, more especially an attempt to test, as critically as microscopic data will allow, the theory of discrete unit characters in color inheritance (discontinuity theory; segregation theory), as opposed to the theory of continuity of the pigment character with interruption of the pigmentation process at various stages. The study involves two incidental problems: (1) Source of the epidermal pigment, (2) cause of degree of coloration of skin. These matters must receive consideration first. Then follows a discussion of the bearings of the determined facts on the question of color inheritance in crosses between whites and blacks, or mulattos.

Material.—The material studied comprises 18 pieces of skin taken from near the mid-line of the abdomen, including 5 pieces from full-blooded negros of varying grades of color, 6 pieces from mulattos of various shades, 4 pieces from brunets, 2 from blonds, and 1 piece of pathologically pigmented skin; also a melanotic sarcoma, several pieces of pigmented skin of incomplete history, sections of infant's scalp and eyelid of new-born mulatto. Individuals were classified as blond or brunet according to color of hair. Mulattos were so adjudged in most cases from general appearance, *i. e.*, absence of distinct negro features, *e. g.*, thick lips, flat nose, etc., though in several cases the individual con-

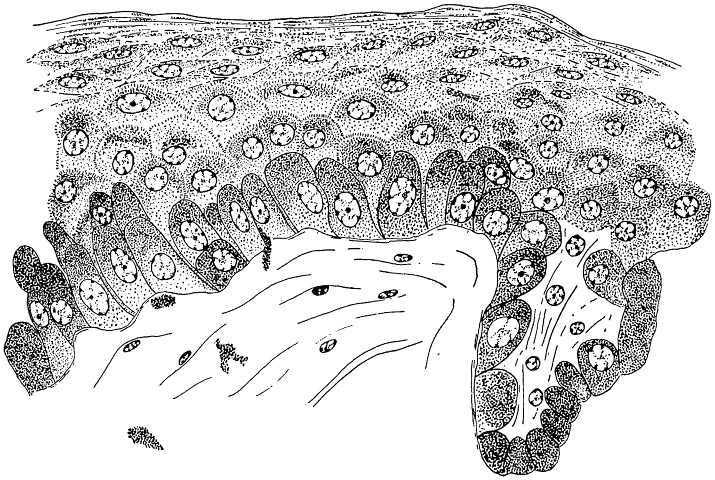

FIG. 1. Camera lucida drawing of unstained section of negro skin (specimen No. 14), showing the distribution of the pigment granules in the epidermis. Nuclei drawn according to their appearance in stained preparation. Dermal pigment cells very much more abundant than would appear from this particular region. The greater height of the basal cells of the rete mucosum Malpighi, as compared with Figs. 2 and 3, due in part to slight obliquity of section. The eleidin and keratohyalin granules of the stratum granulosum not shown. ×750.

tributing the skin admitted to me being "mixed." All but one piece of mulatto skin were tested by the Bradley color top before embedding. In only one case (No. 2) could the individual contributing negro skin be questioned by myself in regard to purity; the remaining four pieces are so classified on the assurance of pathologist and surgeon. Four pieces were tested with the color top. Sections were cut both in celloidin and paraffin, and studied unstained and stained (with 1/12 oil immersion lens) in carbol fuchsin or the hematoxylin and eosin combination. The following is a list of the specimens and the essential points of interest regarding each:

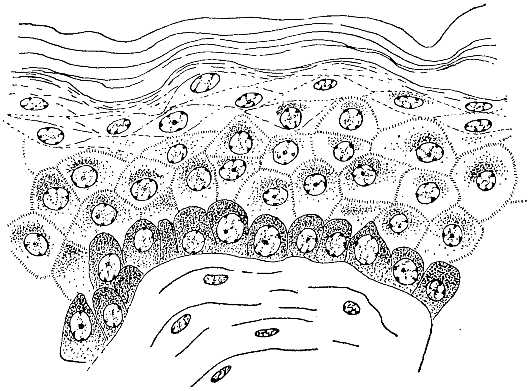

FIG. 2. Drawing of section of light brown mulatto skin (specimen No. 3) showing distribution of the pigment granules in the rete mucosum Malpighi. Darker and lighter mulatto skins differ from this only in the greater and smaller number, respectively, of melanin granules. × 750.

1. Pure negro; from postmortem by Dr. H. Marshall (professor of pathology, University of Virginia); Zenker's fixation; color (matched by mixing yellow, white, red and black on the Bradley color top)—yellow, 4 per cent.; white, 8 per cent.; red, 22 per cent.; black, 66 per cent.

2. Pure negro woman; from abdominal operation by Dr. Harvey Stone (adjunct professor of surgery); fixed in 95 per cent. alcohol; a shade lighter than No. 1.

3. Light mulatto woman; abdominal operation by Dr. Stone; 95 per cent. alcohol fixation; color—yellow, 10 per cent.; white, 18 per cent.; red, 22 per cent.; black, 50 per cent. (Fig. 2).

4. Light mulatto; abdominal operation by Dr. Stone; 95 per cent. alcohol fixation; a shade darker than No. 3.

5. Blond; abdominal operation by Dr. Stone; 95 per cent. alcohol fixation.

6. Pathologically pigmented (grayish yellow) skin of white individual; postmortem (thyroid adenomata) by Dr. Marshall; 95 per cent. alcohol fixation.

7. Brunet; abdominal operation by Dr. W. H. Goodwin (adjunct professor of surgery); 95 per cent. alcohol fixation.

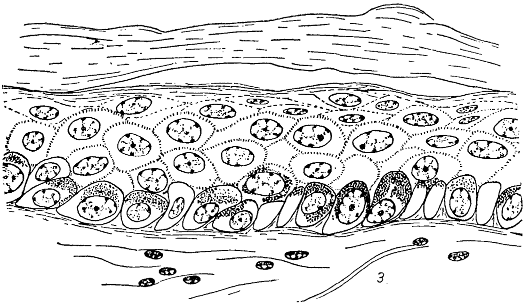

FIG. 3. Drawing of section of skin of blond ("cross between blond and brunet"—specimen No. 13). In lighter blonds (*e. g.*, specimen No. 5) fewer basal cells contain still fewer granules; in darker brunets the basal cells contain more granules. × 750.

8. Light mulatto male (age 80); postmortem (acute cystitis) by Dr. W. Thalhimer (instructor in pathology); Zenker's fixation; color—yellow, 10 per cent.; white, 17 per cent.; red, 30 per cent.; black, 43 per cent.

9. Pure negro; abdominal operation by Dr. Stephen H. Watts (professor of surgery)—95 per cent. alcohol fixation.

10. Brown mulatto boy; abdominal operation by Dr. S. H. Watts; 95 per cent. alcohol fixation.

11. Brunet; abdominal operation by Dr. S. H. Watts; 95 per cent. alcohol fixation.

12. Brunet female (gray); postmortem (goitre and old age) by Dr. W. Thalhimer; Zenker fixation.

13. Dark blond male—age 30 years—("cross between blonde and brunet"); from postmortem (pyæmia and perinephric abscess) by Dr. W. Thalhimer; 95 per cent. alcohol fixation (Fig. 3).

14. Pure negro; abdominal operation by Dr. S. H.

Watts; 95 per cent. alcohol fixation; color—yellow, 5 per cent.; white, 7 per cent.; red, 19 per cent.; black, 69 per cent. (Fig. 1).

15. Pure negro; abdominal operation by Dr. S. H. Watts; 95 per cent. alcohol fixation; slightly lighter than No. 14.

16. Brunet; abdominal operation by Dr. S. H. Watts; 95 per cent. alcohol fixation.

17. Mulatto; abdominal operation by Dr. S. H. Watts; 95 per cent. alcohol fixation; color—yellow, 14 per cent.; white, 14 per cent.; red, 35 per cent.; black, 37 per cent.

18. Mulatto; abdominal operation by Dr. S. H. Watts; 95 per cent. alcohol fixation; a shade lighter than No. 17.

Ranged according to degree of coloration, judged macroscopically, the 17 pieces of skin (omitting No. 6) take the following order:

Negro *9*, *14* (B, 69), *1* (B, 66), *2*, *15*.
Mulatto *4*, *3* (B, 50), *8* (B, 43), *17* (B, 37), *10*, *18*.
Brunet *7*, *11*, *12*, *16*, Blond *13*, *5*.

This list could have been enlarged indefinitely, but more material was not deemed requisite to the demands of this study. Number 6 took rank between numbers 18 and 7.

Sources of Epidermal Pigment.—There are obviously three distinct views which might be held—and as a matter of fact have been held—in regard to the origin of the pigment of the skin: (1) In the epithelial cells of epidermis; (2) in the connective tissue cells of the dermis, and secondarily transferred to the cells of the rete mucosum Malpighi; (3) in both the epithelial and connective tissue cells. The second view more especially further involves the question as to whether the pigment arises in the connective tissue cells as a result of cellular (secretory) activity or whether the cell extracts the pigment (fully formed or unsynthesized) from the blood; also the manner of the transference of the pigment to the epithelial cell.

There are two works which bear upon this point more directly: (1) That of Karg (1888) who ably supports the second view on the basis of findings from a microscopic study of white skin transplanted to a negro and *vice versa, i. e.,* negro skin transplanted to a white individual; (2) that of Meirowsky (1908), who studied the origin of melanic pigment in the skin and eye and, more especially, on the basis of experiments with pigeons and findings in pigmented skin kept alive for several days in a paraffin bath at a temperature of 56 degrees, urges the first view. These two masterly papers advance diametrically opposing views. Karg unqualifiedly put aside the idea that pigment may be formed within the epidermal cell. He says, "Es gelang so, festzustellen, das es nur eines Modus der Entstehung des Pigments giebt. Aus der Lederhaut dringen pigmentirte Zellen in die Epidermis, verästeln sich hier weit und geben ihr Pigment an die Epithelzellen ab," p. 370. Meirowsky describes conditions more in conformity with our later ideas of cellular physiology. According to him, the melanic granules are passed out of the nucleus of the epidermal cell into its cytoplasm, *i. e.,* pigmentation is an intracellular process, both dermal and epidermal.

Historically Riehl (1884) appears to have been the first to describe the condition afterwards interpreted by Karg as supporting his view of epithelial pigmentation, viz., invasion of processes of pigmented connective tissue cells among the epidermal cells. Riehl studied more especially the pigment of hair. He did not generalize, however; and while he thought it improbable, he did not regard it impossible, that pigment may arise out of the protoplasm of epithelial cells. He seems rather to incline to the third view above stated. Moreover, on the basis of findings in a study of three cases of Addison's disease, where the adventitia of blood vessels was richly infiltrated with pigmented cells coincidentally with a hemorrhagic aggregation of red blood cells, he concludes that the pigment arises from the hæmoglobin of the red cells. Aeby (1885) likewise describes the transportation of pigment to the epidermis by wandering cells. Ehrmann (1885–86), who studied the pigmented epithelium of amphibia, differs from Riehl and Aeby only in holding that the pigmented stellate cells of the cutis are non-motile. He describes a network of pigmented cutis cells (chromatophores) connected with the epidermis by processes through which the pigment granules stream into the epithelial cells of the rete mucosum Malpighi. He also concludes that the pigment arises from the hæmoglobin of the red cells, since the pigment cells are most abundant in the vicinity of the blood vessels. The reception of the pigment granules by the epithelial cells he regards a phagocytic process, the epithelial cells being described as corroding the processes and assimilating the contents as part of their own organization. The important observations of Jager (1885) on pigment spots in dog and rabbit after inflammation, and those of R. Krause (1888) on apes, are in substantial accord with those of the afore-mentioned investigators, more particularly in regard to the secondary origin of pigment in the epidermis, and the primary source of the same in the blood. For further information regarding literature of pigment cells, more particularly in the lower vertebrates, the reader is referred to the splendid article by Karg.

It remains to outline more fully Karg's position as representative of the second view above stated. Pigmentation of epidermis and its appendages (hair, etc.) is a secondary process. The pigment is transferred to the epithelial cells through cells which have their origin in the cutis (*i. e.*, chromatophore, Ehrmann). They wander into, or, remaining on border line between epidermis and cutis, send processes into the intercellular spaces of the epidermis. They end in the epithelial cells (capable of a certain amount of amœboid motility) to which they surrender their pigment through process of absorption causing streaming from process to cell. These pigmented cells are wandering cells of the nature of connective tissue cells. They are thought to obtain their pigment from the blood. This, however, is not regarded as hæmoglobin since no red corpuscles are ever seen in these cells. There is here (*i. e.*, in transplanted human skin) no network of pigment cells as described by Ehrmann in amphibia. Nor can the pigment cells be pigmented leucocytes since they have no similarity to the latter, nor are pigmented leucocytes found in negro blood. In the cutis he claims to be able to see all the transition stages between pigment-free connective tissue cells and such as are strongly pigmented. On the basis of his findings he thinks it appears only reasonable that in the pigmenting skin (transplanted white) the earlier unpigmented granules (Reinke's trophoplasts; Altmann's bioblasts) of the chromatophore take on a dark color (by as yet unknown ways) and that this is connected with the presence of blood; and that it can not, however, be regarded as the product of fragmentated red corpuscles. Melanin may be hemosiderin, but is the product of a living cell. His final position thus approaches somewhat to Meirowsky's, though they still differ as to the cell that elaborates the pigment for the epidermis. It is important in this connection to note that while Karg describes numerous branching pigmented connective tissue cells (wandering cells) among the epidermal cells of the transplanted white skin, he failed to find such in the normal skin of the negro. He thinks it probable that such may be found in the skin of the negro embryo.

Meirowsky in his monograph also gives a very complete review of the literature to date. He uses experimental methods mainly. His findings supporting the first view may be briefly summarized: Pigmentation is possible in the epidermis without the agency of "melanoblasts," or even any aid from the cutis. There are both epidermal and cutis melanoblasts, and they are independent of each other. Pigmented epidermal cells are capable, under certain stimuli, to assume irregularly branching forms (filling the intercellular spaces) simulating mesodermal chromatophores (so-called melanoblasts) which might have wandered into the epidermis. This is probably the correct interpretation of Karg's figures. He brings forth cytological evidence to show that the pigment arises from a reddish nuclear substance (a "pyroniuroter Kernsubstanz")—he does not commit himself as to its chemical nature—which passes into the cytoplasm and gradually assumes the yellowish brown color of the melanic granules. These results from experimental procedure are confirmed by findings in the retina of the calf embryo, where the identical stages in pigment formation are observed. He thinks it more probable that the pigment has origin in an albuminous substance (this is in complete accord with the work of Chittenden and Albro—1903) of the nucleus than that hæmoglobin has any contributory rôle. The earlier stages in such a process can be observed in carcinoma without progress to the final stage of pigmentation. This indicates that we are probably dealing with a nuclear substance, which, shed into the cytoplasm, under the influence of an oxidation enzyme, becomes a melanic substance.

As bearing on the point of the origin of pigment my own observations are as follows: No undoubted branching pigmented cells can be seen among the colored epidermal cells in any of my specimens. Occasionally a process of a pigmented connective tissue cell of the cutis is seen to extend for some distance into the rete mucosum Malpighi (Fig. 1). But their number seems very much too meager to supply the pigment of the many colored cells of the epidermis. There is a nice correspondence between the relative abundance of pigmented cells in the dermis and epidermis of the several specimens of skin. In light skins there are few of each type in each layer; in darker skins there is a decided increase in both. But this proportional increase is as reasonably interpreted as due to the same cause influencing both layers, as that the increased number of pigmented epidermal cells demands an increased number of cutis melanoblasts. Moreover, when one considers that there is a continual exfoliation of the superficial layers and a replacing of the same from the lower layers, the number of epidermal pigmented cells in colored skins seems out of all proportion to the number of the cutis melanoblasts which are supposed to furnish the pigment.

The pigment cells of the cutis are most abundant along the border between dermis and epidermis and along the capillaries of the vascular papillæ. This first point would seem to indicate the function ascribed to them by Karg and others, but when one assumes (as all investigators agree in doing) that pigment formation is somehow related to the blood as source of nutrition or supply, the segregation of the pigmented cutis cells at this level becomes intelligible on other grounds, *i. e.*, necessary closeness to the capillaries of papillæ. Only those layers of the epidermis next the border line (*i. e.*, next the capillaries) have the pigment granules of the prevailing size and color for normal pigment cells. Thus my evidence points to a dependence of both cutis and epidermal cells upon the same source (the blood of the capillaries) for a sine qua non of pigment formation, and an independence of each with respect to the other as a necessary source of supply or even as an aid to pigmentation. That the blood constituent is not hæmoglobin the arguments of Karg and the observations of Meirowsky seem conclusively to prove. That it is not an iron-containing element (*e. g.*, hæmosiderin) I have demonstrated by the method of testing with potassium ferricyanide as used by Brown (1910) for the liver. Chemical analysis by Abel and Davis (1896) also has shown that the melanic pigment of the hair and skin of the negro is free of iron. The evidence at hand, as furnished by Chittenden and Albro, von Fürth, Spiegler, Gessard, Riddle, Meirowsky, and others seems to render it very probable that in vital melanogenesis we are dealing with a proteid substance (tyrosin; trophoplast; chromogen) acted upon by an enzyme or oxidase (tyrosinase) and that one (probably the former) is supplied by the cell (nucleus) and the other by the blood.

The fact that the pigment granules, in epidermal cells that are not packed with them, are segregated in the distal portion, indicates that they are responsive to the influence of light. However, the further discussion will not be complicated by a consideration of this possible factor. The following discussion will accept as well supported the position that pigment is formed in the epidermal cells—the analogous formation of pigment in ganglion cells gives further support—by virtue of a cellular metabolism made possible by close association with the nutritive source, *i. e.*, blood vessels.[1]

[1] A specimen of leucoderma from a dark negro obtained at autopsy through the kindness of Dr. W. Thalhimer gives further evidence in support of this position. Macroscopically, the two leucodermic areas, about 5 cm. in diameter, and bilaterally symmetrically placed over the clavicles, appeared perfectly normal except for their very much lighter color (grayish yellow). A section through the transition area shows the following histologic conditions: (1) The leucodermic area contains a comparatively very large number of pigmented cells in the corium. (2) In the epidermis the comparatively small amount of pigment present is confined to some of the columnar cells of the stratum Malpighi. (3) The corium of the pigmented skin has only a moderate amount of pigmented cells. (4) In the epidermis of the normal skin, the columnar cells are laden with melanic granules, and all of the more superficial layers of cells contain a considerable amount of melanic pigment. (5) The pigment granules are everywhere the same in respect to color and size. (6) The epidermal cells appear identical, except for the variable abundance of the pigment granules, in the two regions. In view of the above facts, it seems clear that lack of pigment in the epidermis of the leucodermic patch is not due to a dermal deficiency (supposing the derma to be its source of supply), nor to an inability on the part of the epidermal cells to take up pigment (since they harbor a small amount). These facts speak in favor of the epidermal origin of the epidermal pigment, and indicate a local inability on the part of the epidermal cells to manufacture in normal quantity (for this individual) the melanic granules. Furthermore, interpreting melanogenesis in terms of tyrosin and tyrosinase, the facts indicate a local deficiency or inhibition of one of these factors. It seems more reasonable to suppose that the columnar cells of the epidermis of the leucodermic areas were for some obscure cause (nervous?) unable to elaborate the granules ("pyroninroter Kernsubstanz," Meirowsky) which, under the influence of an oxidase probably everywhere present, turn melanic.

The recent work of Dyson ("An Investigation on Cutaneous Pigmentation in Normal and Pathological Conditions," *Journ. Path. and Bact.*, 15: 3, 1911) in the main also confirms Meirowsky's findings regarding the nuclear origin of the melanic granules in the epidermis of pigmented skins (after treatment with the Finsen lamp). Dyson describes "blue granules which owe their staining capacity (in hæmatoxylin) after bichromating to the presence of an unsaturated fatty substance," very similar to the "pyronin-red substance" of Meirowsky. These granules Dyson regards as "the mother substance of pigment. These granules are complex in character, being composed of a lipoid and proteid element; the proteid portion precipitates out after its escape from the nucleus and remains as a foreign body in the cytoplasm of the cell; whilst the larger granules seen at the periphery of the cells I regard as the lipoid substance after the separation has taken place; these granules then escape into the intercellular lymph spaces" (p. 314). The "pyronin-red" substance he interprets as "probably the chromatic proteid portion of the complex granules from which the lipoid portion has been dissolved by his (Meirowsky) method of preparing his material," *i. e.*, use of alcohol (p. 316). In origin melanotic pigment is then a lipochrome, the melanin being the chromatic proteid portion after

Cause of Degree of Coloration.—Theoretically at least six possibilities are conceivable: (1) Number of pigmented epidermal cells, or, indirectly, (2) number of pigmented connective tissue cells of cutis, (3) number of pigment granules in pigmented epidermal cell, (4) coloration of granules in pigmented epidermal cells, (5) numbers 1 and 3, (6) combination of 1 or 3 and 4, or a combination of the three. It is also theoretically possible that a difference in the size of the granules may play a part in determining the degree of coloration. In view of what was said under the previous heading, number 2 can be disregarded and there remain five plausible possibilities. Which "possibility" or set of possibilities expresses the reality will become clear from the description of the several types of skin. In anticipation of ensuing results it may be said in brief that there seems to be only one factor in skin coloration, viz., the number of the pigment granules, a greater number of granules of course involving a greater number of cells—with a small and possibly negligible variation in size.

DESCRIPTION OF NEGRO SKINS

The several samples of skin will be described in the order of their degree of coloration as seen from the surface. This agrees almost absolutely with the degree (*i. e.*, quantity) of the pigmentation factor, as will appear below.

its separation from the complex lipoid granules. In several points my findings in leucoderma do not accord with those of Dyson: (1) While it may be true that the pigment granules of the cutis cells are slightly coarser, I can not regard them as darker than those of the epidermis. (2) In no case have I been able to discern melanic granules in the nuclei (studied in *unstained* preparations). (3) I find a greater relative amount of cutis pigment in the specimen of leucoderma, whereas Dyson reports no pigment in the cutis of his two samples of leucoderma. (4) Consequently (and for still other reasons) I can not accept his position that cutis pigment is secondary to epithelial, *i. e.*, that pigment passes from epidermis via lymph channels to the derma where it is supposed to be taken up by wandering cells. If this were true the cutis underlying the more highly pigmented epithelium should contain relatively (to leucodermic area) more pigment. But just the reverse is the case in my specimen. In fact the amount of pigment in the epidermis would seem to be too meager to supply the cutis pigment present under the leucodermic patch. All the evidence indicates that the path of pigment transportation is from depth to surface of epidermis.

All the samples being taken from the same body region, there is a very close correspondence in the number of epidermal layers involved.

Number 9: Here all the epidermal strata of cells are pigmented. In the basal layer the cells are packed with the yellowish brown spherical granules to such an extent as partially to obscure the nucleus and cause the cell to bulge. In the more superficial layers, the granules are massed distally and more scattered proximally, the nucleus appearing very prominently. In the cutis, chromatophores are abundant, their granules being similar in shape, size and color to those of the basal epidermal layer. These cells are always in the near vicinity of the blood vessels. In the upper layers of the epidermis the pigment granules become darker, finer and frequently of oblong shape. These several differential features are ascribed to the several factors of desiccation, pressure and keratization that the containing cells undergo in their passage to the exfoliating surface. The same explanation probably (at least to some degree) applies to the invariably darker bacillary pigment granules of the shaft of the hairs appearing in all of the sections of this first group.[2] In sections of child's scalp, however, both shaft and bulb contain the same yellowish-brown granules as found in the skin, the only appreciable difference being a considerable irregularity in shape and size. It must be noted here that not all the basal cells (though in negro skin the exceptions both in dermis and epidermis are rare) are equally packed with granules. The optical effect of a small number of granules is a lighter shade of brown than that given by a denser mass of identically colored granules.

The objection may be raised that discrimination or lack of discrimination between a darker and lighter pigmented granule is the result of an interpretation where the " personal equation " may factor largely. It is not denied that it is difficult to satisfy oneself absolutely that the granules of the various basal cells of the same and different samples of skin are of identically the same color (the color difference between the skin pigment granules and those of the sections of attached hair is decided enough) but all possible caution was observed to offset the personal factor. In short, when the writer after much study was still somewhat undecided as to a definite stand, the slides were shown to three different professors, all with long training and much experience in the use of the microscope. These men were asked to answer the following questions with respect to the basal cells of the eighteen samples, and this without knowledge of what the other men had written: Are the pigment granules of the samples of skin of the same color or of different colors? Name the color or colors? The replies were uniform in recognizing only one type of granules, and in describing it as "yellowish brown," "brownish yellow" and "a dark golden or yellowish brown—amber—somewhere between brass and copper," respectively. One man noted the slightly darker shade of the granules of the more superficial cells.

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[2] I have recently found a very striking exception to the usual brown color of melanic pigment under ordinary conditions in certain cells of young turtles (ca. 25 mm. stage of development). Here growing and dividing cells of the choroid, epidermis, connective tissue generally, and bone marrow contain absolutely black pigment granules.

Number 14 (Fig. 1): All the layers are again pigmented, but there is a slightly smaller amount in the upper layers than in number 9. The pigment cells of the cutis are here somewhat more numerous, showing many anastomosing processes, and forming in places a network of pigmented strands just beneath the scarf skin. A variation in amount of pigment in different regions of the basal layer is again evident. The deeper color of number 9 as compared with 14 seems due to the greater amount of pigment present in the superficial layers.

Numbers 1 and 2 are very like the foregoing except that there is a slight decrease in the number of greatly packed basal cells.

Number 15: This sample shows a quite appreciably smaller number of pigment cells in the epidermis and a yet more pronounced decrease in the corium.

Description of Mulatto Skins

Number 4: The number of granules in the great majority of the basal cells of the epidermis is somewhat less than in the last of the foregoing group. Cells also now appear in the lower layers with only relatively scattered granules. There is an almost complete absence of granules from the cells of the superficial layers. There are decidedly fewer pigmented cutis cells. Hair in section again shows the same sort of pigment granules as above described. This statement holds good for hair wherever they have appeared in these sections (not seen in the samples of blond skin).

Number 3 (Fig. 2): The pigmented basal cells of this specimen contain still fewer granules than in number 4. The very small number and size of the chromatophores of the corium is striking. Here again only the cells of the rete mucosum Malpighi contain the granules.

Number 8 is almost identical with number 3.

Number 17 is like number 8 with slightly less pigment in the rete mucosum Malpighi; but here the superficial layers again contain a considerable quantity of melanin granules and the melanic cutis cells are more abundant than in numbers 3 and 18.

Numbers 10 and 18 are both very like number 8, showing only a slight decrease in the quantity of pigment.

This seems the best place for a brief discussion of the foregoing facts. What is the fundamental cause of the difference in the degree of color of the skins described? Plainly, I believe, a difference in the abundance of the pigment granules in the basal cells of the rete mucosum Malpighi. A densely packed mother cell of this layer gives rise to two daughter cells of very similar constitution which are only slightly altered as they pass to the upper layers. Hence in skins where the basal cells manufacture much pigment, the entire rete mucosum Malpighi, formed of its descendants—the factors of desiccation and cornification not being able at once to produce a very appreciable destruction or modification of the granules—will appear pigmented. But between negro and mulatto skin there does not seem to be any apparent difference as to the number of epidermal cells producing pigment, but only as to the quantity of pigment produced by the same basal cells, an initial greater quantity determining a secondarily persisting greater quantity, and thus an apparently greater number of epidermal pigmented cells. Probably also, the cells generally of the rete mucosum Malpighi retain in small degree the property of the basal mother cell to produce pigment granules.

Description of Skin of Brunet

Number 6 (pathologically pigmented skin): Here one is unable to determine just how much pigment is due to the normal (" midway between blond and brunet ") and how much to the pathologic condition ("thyroid adenomata" —"gall stones, but not jaundiced"). The specimen contains fewer granules than number 18 and more than number 7.

Number 7: Here the granules are very few in number and confined exclusively to the basal layer. There is great variation in the number of granules held by the basal cells. Only very rarely does a small pigmented cutis cell appear in the sections.

Number 11 has still fewer granules than 7 and

Number 17 shows only occasional cells of the basal layer slightly pigmented (few melanin granules).

Number 16 is more like the blond skin to be described. There are very few granules in only occasional cells; and no pigmented cutis cells are seen in the section. This skin could not be told from blond.

Description of Blond Skin

Number 13 (Fig. 3): Here the layer of distinctly pigmented basal cells is fairly complete. The section is very like number 7 of the brunet series.

Number 5 is almost identical with number 16. The pigment granules are very rare; and only a few to a cell.

It must be emphasized at this point that the melanic granules of number 5 are in point of shape, size and coloration indistinguishable from those of number 9.

There is a continuous gradation in color (and the number of pigment granules) from negro to blond skin with an overlapping at the extremes.

The melanic granules of the specimen of melanotic sarcoma were of the same yellowish-brown color (perhaps of a trifle lighter shade), but of very irregular shape and with great variations in size (the larger "granules" may be the result of fusion of smaller masses).

STATEMENT OF RESULTS AND RELATED FACTS

The facts whose interpretation is sought in terms of some principle of heredity are these: (1) The degree of skin coloration is due to the variable number of pigment granules in the cells of the rete mucosum Malpighi involving incidentally a variable number of more superficial cells. (2) The pigment granules (melanic) of all skin (albinos excepted) are identical in size (practically), shape and color (without qualification). (3) The ascending scale of morphological conditions paralleling a progressively deepening grade of pigmentation may be described as follows: (*a*) few cells of basal layer pigmented with few granules—blonds, (*b*) more cells containing more granules—brunets, (*c*) a more or less complete basal layer of cells with many and very many melanic granules (mulattos), (*d*) the cells of basal layer packed and distended with pigment granules; the cells of the more superficial layer also with very many granules.

Or, restated and explained, (4) The progressive increase in progressively darker skins both in the number of granules and in the number of the pigmented cells. That these two facts are related to each other as cause (number of granules) and effect (number of pigment cells) is strongly indicated by the fact that in light mulatto and brunet skins, where only the basal cells are distinctly pigmented, the number of granules per cell in general decreases with the progressively lighter shades.

(5) The results recently published by the Davenports showing a segregation of the original skin colors (grandparental colors) among the individuals of the third generation, *i. e.*, children of mulatto parents.

(6) The accumulation of the pigmented cells near the border line between the dermis and epidermis or in the vicinity of the blood stream.

(7) Melanin formation is an intracellular metabolic process going on independently and in a measure proportionately in both dermis and epidermis. This seems demonstrated by the researches of Meirowsky and others,

and the view is indirectly supported by the comparative findings above described, viz.: (*a*) absence of connective tissue cells (chromatophores) among the epidermal cells (admitted by Karg for normal negro skin), (*b*) comparative rarity of pigmented processes from cutis cells, and (*c*) an apparently disproportionate number of chromatophores as compared with the epidermal pigment cells.

(8) The agreement between the cytologic facts of Meirowsky and the chemical results of Chittenden and Albro, and others, that the antecedent of melanin is some form of proteid.

(9) The observations of Meirowsky showing a passage of granules from the nucleus to the cytoplasm as the initial step in melanogenesis, and a progressive coloration of these granules to a final stage of yellowish-brown pigment.

(10) The production of artificial melanins (''melanoidins''—Schmiedeberg) by Chittenden and Albro and others from ''antialbumid'' and various proteids, and the results described by Spiegler and Riddle and others indicating an interaction of a chromogen (tyrosin compound) with an oxidizing enzyme (tyrosinase) in the formation of melanin.

Discussion

There appears, then, proximately to be only one factor in skin-pigmentation, viz., the number of granules of identical shade (yellowish-brown), incidentally the number of cells containing such granules. The granules would seem to be the result of intracellular activities (Meirowsky) and to have origin in cell proteids (Chittenden and Albro, and Meirowsky). In terms of chromogen and oxidase, the granules may be thought of as tyrosin which under the influence of tyrosinase from the blood or tissues generally becomes melanic.

The melanogenetic process seems to stop at the same point in all grades of colored skin, from negro to blond—in hair of the same it may possibly proceed slightly further, though even this seems doubtful in view of appearances in the hair bulb. One seems to be dealing, then, with a continuous process, *i. e.*, the production of melanic granules; and the numerical point at which the process stops determines the color of the skin. But thought of in terms of greater and lesser ability for tyrosin production (intervention of a tyrosinase-producing factor would modify the results, but not fundamentally alter the mechanism of inheritance); and attributing such factor to a specific cell-organ which may be a chromosome or part of such ("teleomorph"—Spillman), the segregation noted by the Davenports becomes as intelligible as other Mendelian phenomena. From the standpoint of the number of granules some mulatto skins are certainly different from a "blend" between negro and white, and this is true in the direction both of more and of less—from the standpoint of the amount of pigment some mulattos are identical, on the one hand, with negros and on the other with brunets—and evidences a measure of segregation of "strong melanogenesis" and "slight melanogenesis."

A plausible interpretation of Karg's experimental findings might be made on the basis of a larger and smaller amount of tyrosinase in negro and white blood, respectively—or more likely perhaps on the basis of more and less pronounced stimulation by negro and white blood, respectively, to tyrosin production.

The occurrence of melanotic sarcomata in albinos and white horses forces the assumption that in both cases tyrosinase is present, as in ordinary colored animals. In albinos there is evidently an absence generally of tyrosin in usual events (production of tyrosin locally accords better with our present knowledge than a hypothesis of local tyrosinase production). If Spiegler's view represents the veritable condition, viz., that in white horses there is present a white melanin—rendered quite doubtful by Gortner's recent work—the end-result of an oxidation process of tyrosin, the presence of melanotic tumors in white horses may be explained in the same way as in ordinary cases, as shown by the work of Gessard.

Accordingly, when one considers the question of color inheritance among crosses between ordinary white individuals and albinos, two factors (at least—these most prominent and apparently most important; a "multiplicity of units" or factors may be involved in color-inheritance as the Davenports suggest) appear to be involved, *i. e.,* a tyrosin-producing factor and a tyrosinase-producing factor, one at least a function of the epidermal cell, and both having as likely a chromosomal representative (a "teleomorph"—Spillman) as any other cell organ or function. The tyrosin-producing factor is probably generally absent in albinos, locally appearing abnormally in tumor cells, hence two albinos can never produce colored offspring, as amply shown by the results of the experimental breeders.

The observations of Stedman, reported by Bateson (p. 227) "to the effect that an albino negress married to a European had children all mulattos" does not necessarily imply that the factor determining the blackness of the negro (tyrosin production) was carried by the albino. Mulattos are frequently so classified on the basis of marks other than color of skin. Many mulattos are no darker than many white brunets. In the above case the factor controlling tyrosin production may very well have been contributed by the father alone. This instance does not necessarily controvert the assumption that albinos lack the factor of tyrosin production.

Moreover, crosses between albinos and pigmented individuals result in families where albinism greatly preponderates, as shown in the recent "dissertation" by Stainer. In crosses between whites and blacks one deals apparently more especially with the factors of great and small capacity for tyrosin production—tyrosinase being probably of more general distribution. Judging from the pedigrees published by Stainer, absence of capacity for tyrosin production (albinism) in man behaves more like a dominant character (or at any rate, not like a pure recessive) to the presence of such capacity. This is not in accord with the results of the Davenports, which seem to indicate that "internal conditions that lead to deeper pigmentation dominate over the weaker conditions"; similarly as regards color of hair and eyes, "the more pigmented condition tends to be dominant over the less pigmented" according to the earlier investigations of Holmes and Loomis as well as the more recent work of the Davenports. Nor does it accord with the results of the experimental breeders with lower mammals. It may, of course, be found that all mammalian albinos have the white pigment (melanin) described by Spiegler for white horses. Such a result would seem to correlate a number of apparently discordant facts. It would obviate the further assumption of an ''antioxidase'' suggested by Gortner, and render more intelligible the nonrecessive behavior of human albinism.[3] No theory of color-inheritance is satisfactory that can not embrace all the facts of albinism, and such is the present state of affairs.

In crosses between whites and negroes there is generally a partial dominance of the deeper pigmented condition over the lighter in the second (mulatto) generation; the third generation showing a measure of segregation of the original colors. The partiality and incompleteness of dominance and segregation may be due to a ''myriad'' other factors modifying and obscuring more or less the final results.[4]

Seeing that we are dealing with only one kind of colored granules, the apparent segregation noted in the families of mulatto parents does not here seem to be due to a condition of unstable equilibrium in the chemical constitutions of the parental melanin and an attempt at readjustment to an original state of greater stability, as suggested by Riddle.

The apparent continuity of the melanogenetic process, as seen in the continuous numerical gradation of the same colored pigment granules where a graded series of skins is examined, rests, in fact, where single families of mulattos are considered, upon discontinuities or discrete

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[3] In the second part of Davenport's paper on ''Heredity of Skin Pigmentation in Man'' (AM. NAT., Vol. 44, No. 528) is presented an array of facts, drawn from a study of a large number of albino families, that furnishes the most cogent argument yet offered for the recessive nature of albinism.

[4] Professor L. W. Lyde, in an article on ''Climate and Racial Skin Color'' (*Contemporary Review*, February, 1911), states his conclusion that ''pigment is latent in all humans and depends for its development on relative action of the lungs and intestines, which is in turn decided by sunlight and humidity.'' On the other hand, Professor J. H. F. Kohlbougge (''The Influence of a Tropical Climate on Europeans,'' *Eugenics Review*, April, 1911) believes that ''there is no reason for assuming that a dark complexion is due to climate.''

"unit characters" controlling conditions of a more and a less numerous production of melanic granules, which conditions conform more or less closely to an alternative mode of inheritance.

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